AD_____

Award Number: W81XWH-10-1-0609

TITLE: Neuromimaging of Brain Injuries and Disorders at Cleveland Clinic

PRINCIPAL INVESTIGATOR: Dr. Stephen Rao

CONTRACTING ORGANIZATION: The Cleveland Clinic Foundation
Cleveland, OH 44195

REPORT DATE: October 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-10-2011	Annual	23 Sep 2010 - 22 Sep 2011

4. TITLE AND SUBTITLE

Neuromimaging of Brain Injuries and Disorders at Cleveland Clinic

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0609

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Dr. Stephen Rao

E-Mail: raos2@ccf.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Cleveland Clinic Foundation
Cleveland, OH 44195

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Blast injuries are the leading cause of injury in the Afghanistan and Iraq wars. It is unknown whether the neural and cognitive sequelae of blast-related traumatic brain injury (TBI) differs from those resulting from mechanically-induced TBI commonly observed in civilian accidents. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions. Functional MRI is an imaging method that detects increases in cerebral blood volume, flow, and oxygenation that occur locally in response to increased neuronal activity. Recent work has shown that fMRI is capable of measuring synchronous spontaneous low-frequency BOLD fluctuations (LFBFs) in the human brain during a state of alert rest. These spontaneous fluctuations are correlated in brain regions with a high degree of connectivity. The LFBF measure of functional connectivity within the brain is proving to be a powerful and sensitive measure of pathology in a number of patient populations that have previously been difficult to study with other imaging methods. We have recently demonstrated that LFBF measured functional connectivity can be combined with a structural measure of connectivity, MRI based diffusion tensor imaging/tractography, to enhance understanding of neuropathology in a patient population (Multiple Sclerosis).

15. SUBJECT TERMS

Blast-related traumatic brain injury (TBI), fMRI, DTI, cognition

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Introduction

Blast injuries are the leading cause of injury in the Afghanistan and Iraq wars. In a study with Marine and Navy personnel wounded in action in Iraq during a one-month period in 2003, approximately 50% of the injuries were due to explosive devices. In an army medical facility, explosive devices and mortar were responsible for 88% of the wounded. Primary blast injuries occur when changes in atmospheric pressure cause organs containing air, such as the lung, bowel, and inner ear, to rupture. While the effects of primary blast on the brain have been considered to be the result of ruptured air emboli in blood vessels, primary blast may cause damage to the brain via other mechanisms. For example, blast to the abdomen may transfer kinetic energy from blast overpressure to the central nervous system via major blood vessels. Secondary blast injuries are caused by objects set into motion by the explosion, i.e., missiles, hitting people. Tertiary blast injuries are due to the whole body being set into motion by changes in air pressure and hitting objects. Quaternary, or miscellaneous, blast related injuries include crush injuries due to collapsed objects, burns, and smoke inhalation. TBI can result from any of these categories of blast injury. While physiological and other effects of secondary and tertiary blast injury may be similar to those in mechanical TBI due to falls or motor vehicle accidents, effects contributed by primary blast to TBI are less known, although some similarities, such as edema and oxidative stress, common to mechanical TBI have been suggested in animal models. More than 50% of blast-related TBI fall within the mild to moderate severity range.

It is unknown whether the neural and cognitive sequelae of blast-related TBI differ from those resulting from mechanically-induced TBI commonly observed in civilian accidents. The pathophysiological mechanisms associated with TBI most commonly include bleeding, direct tissue damage, and diffuse axonal injury (DAI). The presence of a penetrating injury or intracerbral hemorrhage defines the severity of a TBI as at least moderate, but DAI can occur in the milder injuries. DAI results when sudden acceleration/deceleration and angular momentum forces cause shearing or stretching of axons, which can lead to impaired axonal transport. The microscopic result is the appearance of focal axonal swellings and subsequent axonal degeneration. DAI is common after closed head injuries and most commonly affects tracts at gray/white matter junctions, particularly in the frontal and temporal regions, but is often invisible on standard structural MRI. Understanding the potentially unique sequelae of blast-related TBI is critical for accurate diagnosis and designing effective pharmacological and neurorehabilitation interventions. A major goal of this project is to use advanced neuroimaging techniques and computerized neuropsychological assessment to determine if the long-term (> 12 month post-injury) brain sequelae associated with blast-related mild-to-moderate TBI (MTBI) can be distinguished from sequelae associated with civilian MTBI. To our knowledge, no such study has been reported in the literature.

Body

Year one of the project was devoted to the development of the necessary infrastructure for the execution of this study. A number of development tasks have been undertaken to develop the staff and personnel for the study, develop the cognitive and computational tasks, and to establish and validate the reliability of the imaging infrastructure to conduct the study. All of these goals have been accomplished and the accrual of subjects is beginning. While there have been

problems over the year, each of them has been successfully managed to the exacting standards of the Principal Investigator. This meticulous work has laid the groundwork for high integrity in data collection. Details regarding each of these tasks are provided below, broken down by category.

Institutional Review Board approval

The Cleveland Clinic provided provisional approval of the project on 12/17/2010, pending approval by the United States Army Medical and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). The proposal was promptly submitted to USAMRMC-ORP-HRPO on 12/20/2010. We did not hear any response to this submission until the PI made an inquiry of Lori Walther, the Human Subjects Protection Scientist (USAMRMC-ORP-HRPO) on 3/24/2011. Multiple submissions were required to address concerns of the USAMRMC-ORP-HRPO over a six month interval. It should be noted that the PI made prompt responses to each critique of the proposal by USAMRMC-ORP-HRPO. Final approval from USAMRMC-ORP-HRPO came on 8/29/2011. Thus we were unable to recruit subjects until the 12th month of the first year of funding.

Subject recruitment The detailed flow chart of recruitment procedures has been completed. The final version of the procedural manual for the screening and outcome measures is completed. Despite the lengthy delay in being able to recruit subjects due to the lack of USAMRMC-ORP-HRPO approval, we were able to recruit a total of 16 subjects (3 milMTBI, 4 milOI, 4 civMTBI, and 5 civOI) during the final month of the first year funding period. Given the pace at which we have been able to recruit subjects, we do not anticipate reaching our goal of 60 participants. However, because of the lengthy delay in obtaining USAMRMC-ORP-HRPO approval, we may require a no cost extension to complete the work.

Staff recruitment, employment, organization, training. We have hired all required personnel and general orientation and human subjects training was completed for all employees. Training on the administration of screening and behavioral tasks has been completed.

Neuropsychological and Neurobehavioral procedures

- All tasks were readily identified and purchased, including the ANAM (computerized neuropsychological test battery) and the computerized version of the Structured Clinical Interview for the DSM-IV (SCID).
- A task manual, including instructions, procedures, scoring materials and data dictionary was created.
- We developed a comprehensive database for the recording of neurobehavioral and neuropsychological data.

MRI

- FMRI Task Development: The FMRI motor task for this project was programmed for use in the scanner using the Presentation software platform.
- Brain Imaging Protocols: All imaging pulse sequences, including whole brain LFBF, DTI, T1, 3D SPACE T2, 3D SPACE FLAIR, fMRI, are evaluated through weekly QA procedures.

- A protocol for managing the imaging data as it is collected was established, identifying the staff involved in each step of data analysis, agreeing upon integrity checks for the imaging data, and outlining a timeline for the processing of data.

Key Research Accomplishments

At this point in the project, the key accomplishments have been the development of the infrastructure for conducting the research with the highest possible degree of consistency and integrity between the two sites. With this solid foundation, we are in position to begin data collection and analysis. The subjects we recruit for the study will be extremely well characterized and matched across groups, based on the integrated involvement of our staff in the recruitment clinics. We anticipate a productive and efficient process based on the painstaking and meticulous work that has been put in to this point. To summarize, the key accomplishments have been:

- Recruiting and training staff to conduct the study
- Development of the neuropsychological test battery and training on neurobehavioral examination methods
- Development of computerized cognitive assessment battery
- Development of the fMRI activation task.
- Approval by the CCF institutional review board and USAMRMC-ORP-HRPO (albeit delayed).
- Development of a recruitment infrastructure to support accurate subject identification and characterization.
- Recruitment of 16 subjects in less than one month

Reportable outcomes

Given that the initial goals have been to develop the mechanisms by which we will conduct the project, the products of our labor are not yet tangible. The data from this project will be flowing in over the next 1-2 years, generating reportable outcomes. We have spent the time over this carefully attending to detail, ensuring the integrity and reliability of the data we will use to arrive at those outcomes.

Conclusion

The first year of the project has been devoted to creating a viable infrastructure to support the collection of data across multiple sites. We have dealt with numerous challenges, some anticipated, some unanticipated. In each case, through the dedicated work of project staff, we have successfully resolved the problems and achieved our goals. We are satisfied that we are beginning the accrual of data that will be of high reliability and integrity. Over the next 1-2 years, we will enroll the planned 60 subjects.

References

Given that we are not yet reporting data, we have no references at this time.

Appendices: None at this time